

50. (New) The method of claim 41 wherein step (c) comprises assessing the type of brain injury wherein the presence of a brain endothelial protein and one or more proteins selected from the group consisting of MBP, S100, and NSE at statistically significant concentrations is evidence that said brain injury is a cerebral infarction.

51. (New) The method of claim 41 wherein step (c) comprises assessing the type of brain injury wherein the presence of MBP at a concentration of greater than about 200 times the normal level is evidence that said brain injury is an intracerebral hemorrhage.

52. (New) The method of claim 41 wherein step (c) comprises assessing the type of brain injury wherein the presence of S100 at a statistically significant concentration is evidence that said brain injury is a cerebral infarction or a subarachnoid hemorrhage.

53. (New) The method of claim 41 wherein step (c) further comprises assessing the type of brain injury wherein the presence of S100 and NSE at a statically significant concentration and the absence of any other markers is evidence that said brain injury is a subarachnoid hemorrhage.

*AI  
concluded*

---

#### REMARKS

##### Response to Restriction Requirement

According to the Office Action, the Applicant must elect one of the following inventions for further prosecution:

- Group I. Claims 21-34, drawn to a method for the differential diagnosis of ischemic and hemorrhagic cerebral events, determining brain injury, assessing NSE, endothelial cell membrane protein, MBP, and S100.
- Group II. Claims 21-33 and 35, drawn to a method for the differential diagnosis of ischemic and hemorrhagic cerebral events assessing brain endothelial cell membrane protein and any other ischemic protein and determining patients for thrombolysis.

- Group III. Claims 21-33 and 36, are drawn to a methods for the differential diagnosis of ischemic and hemorrhagic cerebral events assessing S100, increasing concentration of NSE, absent the presence of brain endothelial membrane cell protein, and determining patient's for thrombolysis.
- Group IV. Claims 21-33 and 37, are drawn to a methods for the differential diagnosis of ischemic and hemorrhagic cerebral events assessing S100 and/or increased concentrations of NSE or brain endothelial membrane cell protein thereby determining patient's for thrombolysis.
- Group V. Claims 21-33 and 38, are drawn to a methods for the differential diagnosis of ischemic and hemorrhagic cerebral events measuring S100 and MBP to determine severe cerebral edema.
- Group VI. Claims 21-33 and 39, are drawn to a methods for the differential diagnosis of ischemic and hemorrhagic cerebral events measuring NSE and any other protein measuring evolving cerebral infarct, further measuring brain endothelial cell membrane protein to determine patient's for thrombolysis.

In response to the requirement of restriction of claims, Applicant elects with traverse to prosecute the subject matter of Group I, claims 21-34 drawn to methods of determining brain injury, diagnosing ischemic and hemorrhagic cerebral events, and assessing the concentrations of NSE, brain endothelial cell membrane protein, MBP, and S100. Applicant traverses the Restriction Requirement on the grounds that the groups are interrelated and a search of the claims of Group I would necessarily include a search of the claims of Groups II-VI.

#### Claim Amendments

Claims 35-39 are cancelled without prejudice. New claims 40-53 are introduced. The new claims which are drawn to methods of determining brain injury, diagnosing ischemic and hemorrhagic cerebral events, and assessing the concentrations of NSE, brain endothelial cell membrane protein, MBP, and S100 fall within Group I. Applicant submits that the new claims

are fully supported by the application as filed. No new matter has been introduced by the new claims. Upon entry of this amendment claims 21, 23-34 and 40-53 are pending.

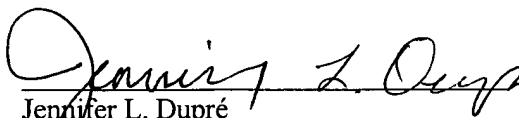
### CONCLUSION

Applicant believes that the subject matter of the pending claims is patentable and that the instant application should be allowed. If the Examiner believes that a telephone conversation would expedite prosecution of this application, the Examiner is urged to contact the undersigned.

If there are any charges, or any credits, please apply them to Deposit Account  
No. 07-1074.

Respectfully submitted,

Date: August 31, 2001

  
Jennifer L. Dupré  
Registration No. 41,722

GENZYME CORPORATION  
Legal Department  
15 Pleasant Street Connector  
P.O. Box 9322  
Framingham, MA 01701-9322  
Attention: Jennifer L. Dupré  
Telephone: (508) 270-2559  
Facsimile: (508) 872-5415